SYNTHESIS OF SOME N-SUBSTITUTED MALEIC IMIDES.

By B. MATKOVICS, L. FERENCZI and GY. SELMECZI[1]

Institute of Organic Chemistry, The University, Szeged

(Received September 28, 1958)

A two-step synthesis was evolved by the authors for the preparation of N-aryl and N-allyl maleic imides, yielding in most cases the desired end products. This way of synthesis is of appreciable importance, due to the great biological activity of N-substituted maleic imides as -SH inhibitors. Besides, N-substituted maleic imides are essential initial substances in the pharmaceutical, dye and plastics industries.

VELDSTRA and HAVINGA detected in 1943 the property of coumarine and a great number of other unsaturated lactones to inhibit the growth-promoting effect of naphthyl acetic acid [1], [2]. The compounds investigated by them proved to be —SH inhibitors. Obviously, when in later years substances possessing defoliative properties were needed, they were sought in the first line amongst the —SH inhibiting compounds [3].

In these investigations, N-phenyl maleic imide and its numerous cyclic derivatives proved to be active from this point of view. At the same time, also the mono-, di- and trichloro derivatives of N-phenyl maleic imide, further the N-α-naphtyl, N—2, 4-dichlorobenzyl, N-α-tolyl, N-isopropyl and N-octyl maleic imides were prepared and the activity of these compounds examined by defolative and maize coleoptyl tests. These investigations gave a number of results of interest. It was found among others that, of N—R-maleic imides, N-α-naphthyl maleic imide possesses the strongest activity and that effectiveness disappears in the presence of an aliphatic side chain (N-isopropyl maleic imide being inefficient). According to the investigations, the increase in lipoid solubility encourages the effect. The double bond in the centre of the molecule is an indispensable requirement of activity. *E. g.* on saturation of the double bond (N-aryl succinimides) both tests became negative. The inhibiting effect of maleic imides can be suspended by treating the plants with naphthyl acetic acid or cysteine.

The experimental results indicate that the action of both the —SH inhibitors and of other inhibitors can be reverted by auxin substances, serving as an example of extreme interest of competitive inhibition.

The mentioned example is disclosed by Fig. 1.

---

[1] A part of this paper has been submitted to this Institute by GY. SELMECZI in May 1958 as a contest dissertation.

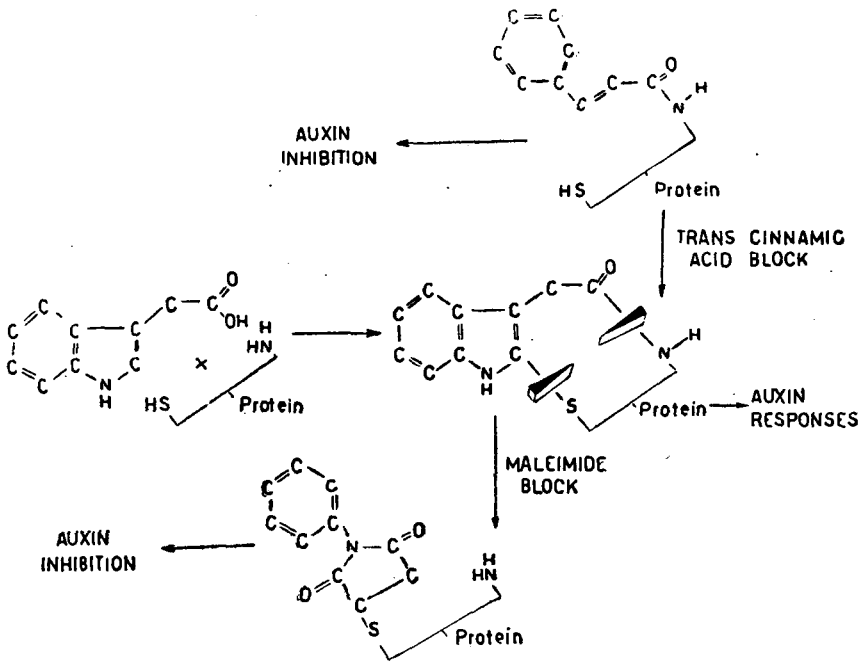

Fig. 1

It appears from Fig. 1 that the various auxin substances act as growth stimulating hormones by being coupled, through their carboxyl group to the amino groups of proteins and, respectively, through their α-carbon atoms to the —SH groups of proteins. However, the protein molecules of plants are made sensitive against various —SH reagents by the presence of various auxins. Trans-cinnamic acid just as various N-phenyl maleic imides remove as —SH reagents the auxins of their sites. Obviously, lipoid solubility plays also a role in that it encourages the passage through the various cell membranes. The inhibiting action of N-phenyl maleic imides is promoted by halogenation as well. However, the promoting effect is, in addition to being correlated with the further decrease of water solubility, influenced also by other steric factors, as *e. g.* of ortho-, meta and para-chlorophenyl-maleic imides the para-derivatives proved to be of the strongest activity. It will we shown later that certain investigations clearing up correlations between effect and structure were carried out by us as well.

A group of English research workers demonstrated in 1948 [4], [5] the inhibiting effect of minute concentrations of maleic imide and of aliphatic maleic N-substituted imides on the growth of chicken fibroblasts. It was found that allyl maleic imides form compounds with $HS \cdot CH_2 \cdot COOH$, $HS \cdot C_6H_4 \cdot COOH$ and glutathion [6], [7]. This formation of compounds proceeds quantitatively to an extent that it can be applied at the detection of substances containing —SH group [8] (Fig. 4, (XII)).

The acid amides obtained as intermediates at the synthesis of N-substituted maleic imides are suitable, under certain conditions, for the synthesis of peptides [9]—[11].

The utilization of acid amides in this field deserves to be discussed here in detail as it includes a great number of possible syntheses of aspartyl peptides. Namely, when maleic anhydride is reacted in the manner shown

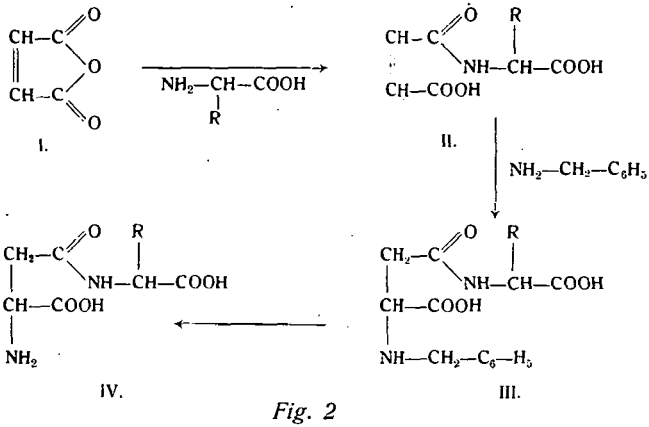

Fig. 2

by Fig. 2, with an aminoacid, an acid amide forms as an intermediate which lends itself to the synthesis of any aspartyl peptide desired (Fig. 2). Our experiments in this direction are in progress.

An interesting way of utilizing maleic imide is its use in the DIELS—ALDER synthesis [12], [13]. In this relation, it has been observed by RAY

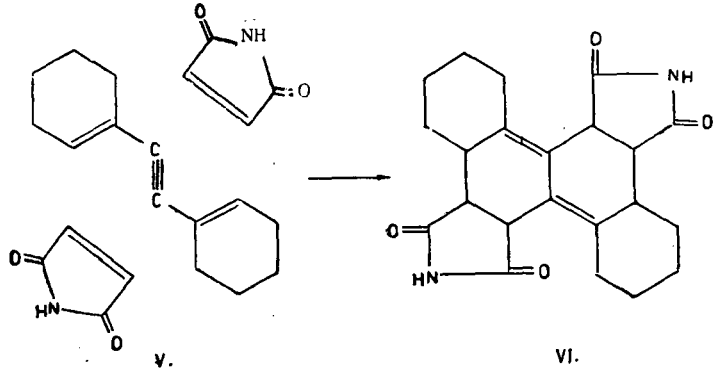

Fig. 3

and co-workers [12] that maleic imide is in DIELS—ALDER condensations more active than maleic anhydride. Thus it can be presumed that many condensations which failed with maleic anhydride can be carried out by success with maleic imide. Accordingly, condensation of 1,1'-dicyclohexenyl acetylene (V) with maleic imide gave $\Delta^{6a7a,\ 1a12a}$-tetradekahydrochrysene-

5, 6, 11, 12-tetracarboxy-diimide (VI) (Fig. 3). KWART and BURCHUK [13], on describing the properties of the exo- and endo-adducts obtained at the DIELS—ALDER condensation of furane and maleic imide, compared them with those of the exo-adduct afforded by the condensation of furane and maleic anhydride. The same investigations should be repeated with pyrrole.

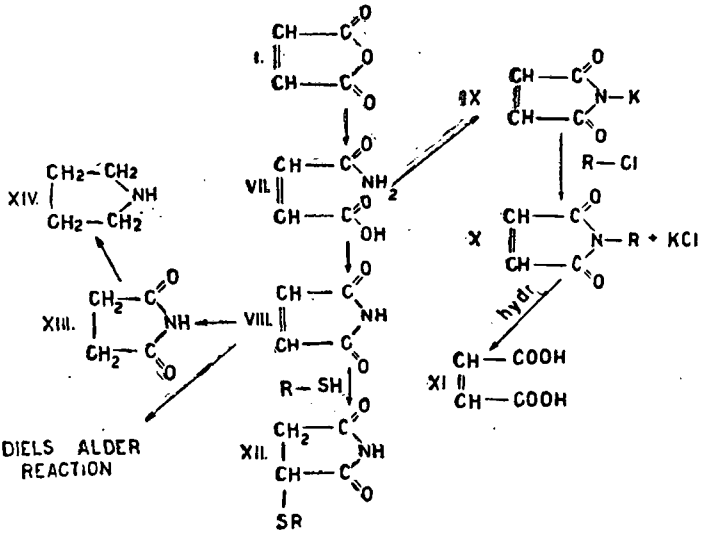

Fig. 4

By preparing the potassium salt of maleic imide, the synthesis of primer amines becomes possible as well, applying the principles of the GABRIEL synthesis. The development of the technique of this way of synthesis is also in progress (Fig. 4, IX, X, XI).

It must yet be mentioned briefly that pyrrolidine and N-substituted derivatives of pyrrolidine can be prepared by saturating the unsaturated bond and subsequently reducing by lithium aluminium hydride, using maleic imide and N—R-maleic imide as initial substances (Fig. 4, XIII, XIV).

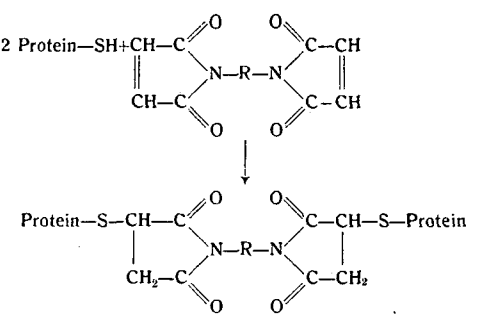

Fig. 5

An application of interest of bis-maleic imides is reported by MOORE and WARD [14], producing with the use of bis-maleic imides cross bonds between proteins of cattle plasm and keratin (Fig. 5).

Maleic imides are similarly applied by the polymerisation dye and drug industries.

Subsequent to the given survey of the application of maleic imide and N-allyl or aryl maleic imides, problems of the chemical synthesis of various N-substituted maleic imides will be discussed.

Methods of preparing N-substituted maleic imides will only be mentioned which were applied by success or which shortly will be tested.

N-phenyl maleic imide was firs prepared by ANSCHÜTZ and WIRTZ [15], on heating malic anilide. Later, it was obtained in better yields under finer conditions of cyclization [16], [18]. The general way of synthesis is a two-step method (Fig. 6). We also chose the two-step synthesis, isolating the formed acid amide.

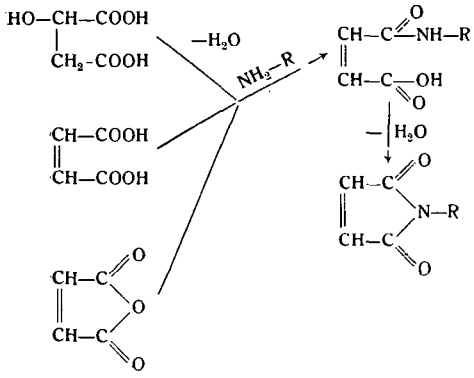

Fig. 6

In our experiments, various anhydrous solvents were used for preparing acid amides, depending on the solubility of the amine component, the other component being throughout maleic anhydride. In the second step, various methods of cyclization were applied which will be described later.

MARRIAN and co-workers [4]—[8] observed that N-allyl maleic imides and various quinones inhibit the growth of cells in chicken fibroplast tests as well as in tests with groups of Gram-positive and Gram-negative bacteria. We also examined the behaviour of a characteristic member of the group of N-aryl maleic imides against various test organisms. N-phenyl maleic imide proved to inhibit already in low concentrations [19] the growth of certain strains of yeasts, fungi and bacteria. However. the poor solubility in water represents a serious disadvantage of N-aryl maleic imides. Some examinations were carried out by us in connection with bacterial tests, in order to prove which of the stuctural element of N-phenyl maleic imide is in correlation with the chemotherapeutic effect observed at relatively low concentrations. On preparing, however, the succinic imide, the phthalic imide and the N-benzyl phthalic imide, neither of them was found to be active in bacterium tests, even when applied in high concentrations. Consequently, the N-phenyl maleic imide structure must be the one securing chemotherapeutic effects. Double bond seems to play an essential role in chemotherapeutic activity. Namely, when the double bond is saturated (succinic imide) or when the double bond becomes a part of a benzene ring (N-benzyl pthalic imide), the substance loses its bacteriostatic activity. Thus, N-aryl maleic imides, similarly to maleic imide, act by binding the —SH groups as already shown by MARRIAN and co-workers [6], [7].

Experimental

Succinic imide [20]: recrystallized from ethanol, m. p. 125°.

Phtalic imide [20]: recrystallized from ethanol, m. p. 234°.

N-*benzyl phtalic imide:* obtained as an intermediate when preparing benzylamine. Recrystallized from glacial acetic acid, m. p. 116° [21].

Maleinanilic acid (I)

The solution of 100 g (1,02 mole) of maleic anhydride in 100 ml of anhydrous methanol, prepared at room temperature, was treated, on cooling by ice, with 94 g (1,02 mole) of freshly distilled aniline in about 30 minutes. Crystals of maleinanilic acid immediately appeared. On allowing the mixture to stand overnight in an ice box, the crystals were filtered and washed with anhydrous methanol. Yield: 126 g (65,6%) of a white powder. Recrystallized from ethanol, m. p. 198°.

Analysis ($C_{10}H_9O_3N$, mol. wt. 191,18): Calculated C 62,83; H 4,71; N 7,33%. Found C 62,81; H 4,35; N 7,20%.

N-*phenyl maleic imide* (II)

On using the same initial substance (the anilide I), we prepared N-phenil maleic imide by various methods. The way applied by ANSCHÜTZ and WIRTZ [15] is of a poor yield. Better yields of II were obtained when using phosphorus pentoxide or acetic anhydride, NaOAc as dehydrating agent as follows.

The mixture of 68,5 g (0,36 mole) of I and 4,4 g (0,033 mole) of phosphorus pentoxide was carefully heated to 100°, under shaking. The substance quickly melted any the temperature rose to 150°. N-phenyl maleic imide of low m. p. was the supernatant above a tar-like polymerized lower layer. On decanting the supernatant, the residue was repeatedly washed with water, then extracted with benzene. The decanted portion was also extracted with benzene, the benzene solutions combined, dried over anhydrous sodium sulphate, clarified by bone black filtered, and benzene removed by distillation under reduced pressure, to yield 61,6 g (66,7%) of crude II. On dissolving the crude product hot in a mixture of 1:9 benzene:petroleum ether, and allowing the liquid to cool, II separated as needle crystals which were filtered. About 70—80 ml of solvent mixture are needed to 1 g of substance. Yield: 24,3 g, m. p. 90°. Analysis ($C_{10}H_7NO_2$, mol. wt. 173,18): Calculated C 69,4; H 4,07; N 8,06%. Found C 69,5; H 4,16; N 8,3%.

2 g (0,02 mole) of I were treated with 20 ml of acetic anhydride and 1 g of freshly prepared sodium acetate, heated to 93° on the steam bath, kept at this temperature for 10 minutes, then poured on ice. Crystals precipitated in some minutes. On filtering, 1,2 g of crystalline substance, m. p. 89—90° was obtained.

Analysis: Calculated N 8,06%. Found N 7,96%.

Maleic-α-naphtilide (III)

Both α-naphtylamine and maleic anhydride were dissolved in choroform in 0,1 *M* concentration, and the precipitate was filtered. Recrystallized from ethanol, m. p. 116—117°. Analysis: ($C_{14}H_{11}NO_3$, mol. wt. 241. 24). Calculated C 69,71; H 4,56; N 5,81%. Found C 69,72; H 4,73; N 6,12%.

N-*α-naphtyl maleic imide* (IV)

On melting 6,7 g (0,03 mole) of finely pulverized III with 1,6 g (0,01 mole) of phosphorus pentoxide at a temperature of about 100—120°, the reddish brown melt washed with water, then the expected product extracted with about 500 ml of benzene, the benzene solution dried over anhydrous sodium sulphate, filtered and evaporated to dryness under reduced pressure. Crude product: 3,85 g (57,5%) of yellowish brown substance which was dissolved hot in 300 ml of a 1:8 mixture of benzene:petroleum ether. Allowing the solution to cool, yellow prisms appeared, m. p. 108°. Analysis ($C_{14}H_9NO_2$, mol. wt. 223,12): Calculated N 6,28%. Found N 6,3%.

Maleic β-naphthylide (V)

The naphthylide was prepared by the way described at the production of III. Its m. p. was 188°, the overall formula and mol. wt. being identical to those of III. Analysis: Calculated N 5,81%. Found N 5,65%.

N-*β-naphthyl maleic imide* (VI)

On refluxing the solution of 1 g of V in 20 ml of anhydrous xylene for 4 hours, the mixture was evaporated. The yellowish brown substance slowly crystallized. On recrystallization, m. p. 148°. Its overall formula and mol. wt. are equal to those of IV.

Analysis: Calculated N 6,28%. Found 6,15%.

Maleic p-*sulphamidobenzoic acid* (VII)

The solution of 11,25 g of sulphamidobenzoic acid in 80 ml of distilled water was mixed with the solution of 5 g of finelly pulverized maleic anhydride in 80 ml of distilled water, allowed to stand overnight in an ice box, the precipitated crystals filtered and dried. M. p. not observable.

Analysis: ($C_{11}H_9NO_7S$, mol. wt. 299,06): Calculated N 4,68%. Found N 5,15%.

N-p-*sulphamido-benzoic maleic imide* (VIII)

Attempts to cyclizate failed so far.

$C_{11}H_7NO_6S$, mol. wt. 281,04.

Maleic p-*aminobenzene sulphonic acid* (IX)

The solution of 5,4 g of p-aminobenzene sulphonic acid in 30 ml of anhydrous methanol was treated with 3,5 g of maleic anhydride, allowed to stand, the precipitate filtered and dried. M. p. 191°.

Analysis ($C_{10}H_9NO_6S$, mol. wt. 271,25): Calculated N 10,26%. Found 10,45%.

N-p-*aminobenzene sulphonic maleic imide* (X)

2 g of IX was kept for 10 minutes at 93° on the steam bath in a mixture of 20 ml of acetic anhydride and 1 g of freshly ignited sodium acetate, then poured onto ice and stirred. On filtering the crystalline precipitate, substance of m. p. 112° was obtained.

Analysis: ($C_{10}H_7NO_5S$, mol. wt. 253,23): Calculated N 11,11%. Found 11.3%.

Maleic p-*aminobenzoic acid* (XI)

On dissolving 8 g of p-aminobenzoic acid and 11 g of maleic anhydride in a mixture of 50 ml of benzene and 30 ml of anhydrous methanol, a white crystalline substance appeared instantaneously. On filtering and drying, m. p. 183°.

Analysis ($C_{11}H_9NO_5$, mol wt. 235,2): Calculated N 5,71%. Found N 5,90%.

N-p-*aminobenzoic maleic imide* (XII)

Attempts to prepare it by the phosporus pentoxide, by the xylene and by the acetic anhidride or sodium acetate methods were unsuccessful, either. $C_{11}H_7NO_4$, mol. wt. 217,18.

Maleic ethyl urethane (XIII)

On adding 5 g of maleic anhydride to the solution of 10 g of ethyl urethane in 50 ml of anhydrous benzene and allowing the mixture to stand for several days, pale pinkish crystals precipitated, m. p, 135—136°.

Analysis ($C_7H_9NO_5$, mol. wt. 187,15): Calculated N 7,03%. Found N 7,5%.

N-*carbetoxy maleic imide* (XIV)

Attempts to cyclizate it failed so far. $C_7H_7NO_4$, mol. wt. 169,13.

Maleic p-*amino-acetophenone* (XV)

On addig, in small portions under cooling, 5 g of maleic anhydride to the solution of 6,9 g of p-amino-acetophenone in 30 ml of anhydrous methanol, and allowing the mixture to stand overnight, yellow srystals precipitated from the dark red liquid. On filtering, 7,5 g of dry crystalline substance, m. p. 276° were obtained.

Analysis ($C_{12}H_{11}NO_4$, mol. wt. 233,06): Calculated N 6,01%. Found N 5,95%.

N-*phenyl-acetophenone maleic imide* (XVI)

On cyclizating 2 g of XV, both quantitatively and qualitatively homogenous substance could be separated, m. p. 151°.

Analysis ($C_{12}H_9NO_3$, mol. wt. 215,2): Calculated N 6,51%. Found N 6,25%.

Maleic p-*toluidine* (XVII)

On adding, under cooling, 4,5 g of maleic anhydride in 10 ml of anhydrous methanol to the solution of 4,5 g of toluidine in 10 ml of anhydrous methanol, the mixture was allowed to stand overnight in an ice box and the precipitated crystals filtered. M. p. 236°.

Analysis ($C_{11}H_{11}NO_3$, mol. wt. 205,06): Calculated N 6,82%. Found N 6,5%.

N-o-*tolyl maleic imide* (XVIII)

Cyclization of 2 g of XV by the previously described acetic anhydride and sodium acetate method afforded a substance of m. p. 71—72°

Analysis ($C_{11}H_9N_2$, mol. wt. 187,05): Calculated N 7,47%. Found N 7,6%

Maleic m-*nitro-aniline* (XIX)

On adding slowly, under cooling, 21 g of maleic anhydride to the solution of 15 g of m-nitro-aniline in 50 ml of anhydrous methanol, the precipitated crystalline substance was filtered. M. p. 197°.

Analysis ($C_{10}H_8N_2O_6$, mol. wt. 236,18): Calculated N 11,86%. Found N 12,02%.

N-m-*nitrophenyl maleic imide* (XX)

The conversion of XIX into XX the acetic anhydride and sodium acetate method afforded in fair yields N-m-nitrophenyl maleic imide m. p. 134°.

Analysis ($C_{10}H_6N_2O_5$, mol. wt. 218,16): Calculated N 13,14%. Found N 12,90%.

Maleic o-*aminophenol* (XXI)

On adding, under cooling, 34 g of maleic anhydride to the solution of 31 g of o-aminophenol in 310 ml of anhydrous methanol, and filtering and drying the precipitate yielded 30,7 g (52,21%) of the substance, m. p.

Analysis ($C_{10}H_9NO_4$, mol. wt. 207. 18): Calculated N 6,76. Found N 6,79%.

N-o-*oxyphenyl maleic imide* (XXII)

XXII was prepared as described former, from 2 g of XXI by the acetic anhydride, sodium acetate method. On filtering, dissolving the product hot in benzene and precipitating with petroleum ether from the benzene solution substance of m. p. 94° was obtained.

Analysis ($C_{10}H_7NO_3$, mol. wt. 189,16): Calculated N 7,41%. Found N 6,96%.

Maleic 2-amino-4-methyl-thiazole (XXIII)

On adding in small portions, under cooling, 5 g of finely pulverized maleic anhydrite to the solution of 5,2 g of 2-amino-4-methyl-thiazole in 10 ml of anhydrous methanol prepared at room temperature, a crystalline substance shortly precipitated. On filtering, it was dried. M. p. 234°.

Analysis ($C_8H_5NO_3S$, mol. wt. 212,23): Calculated N 13,20%. Found 12,98%.

N-*2-methyl-4-thiazole maleic imide* (XXIV)

So far, all attempts to cyclizate it by the tested methods failed.

$C_8H_3NO_2S$, mol. vt. 180,64.

* * *

Thanks are expressed to the Analytical Department of this Institute for carrying out the analyses.

References

[1] *Veldstra, H., E. Havinga:* Rec. Trav. chim. **62**, 841 (1943).
[2] *Veldstra, H.:* Ann. Rev. Plant. Physiol. **4**, 151 (1953).
[3] *van Overbeek, J., R. Blondeau, V. Horne:* Am. J. Botany **42**, 205 (1955).
[4] *Friedmann, E., D. H. Marrian, I. Simon-Revss:* Brit. J. Pharmacol. **4**, 105 (1949).
[5] *Friedmann, E., D. H. Marrian, I. Simon-Revss:* Biochim. Biophys. Acta **8**, 680 (1952).

[6] *Marrian, D. H.:* J. Chem. Soc. **1949**, 1515; 1797.
[7] *Marrian, D. H., E. Friedmann, J. L. Ward:* Biochem. J. **54**, 65 (1953).
[8] *Friedmann, E.:* Biochim. Biophys. Acta **9**, 65 (1952).
[9] *Frankel, M., Y. Liwschitz, Y. Amiel:* J. Amer. Chem Soc. **75**, 330 (1950).
[10] *Liwschitz, Y., A. Zilkha:* J. Amer. Chem. Soc. **77**, 1265 (1955).
[11] *Irsay, R. D., Y. Liwschitz, A. Zilkha:* Bull. Res. Council Israel **617**, 272 (1957).
[12] *Ray, Fr. E., E. Sawichi, O. H. Borum:* J. Amer. Chem. Soc. **74**, 1247 (1952).
[13] *Kwart, H., I. Burchuk:* J. Amer. Chem. Soc. **74**, 3094 (1952).
]14[*Moore, J. E., W. H. Ward:* J. Amer. Chem. Soc. **78**, 2414 (1956).
[15] *Anschütz, R., Q. Wirtz:* Annalen **239**, 137 (1887).
[16] *Searle, N. E.:* US. P. 2,444,536 July 6 (1948).
[17] *Arnold H. W., N. E. Searle:* US. P. 2,462,835 May 1 (1949).
[18] *Kretov, A. E., N. E. Kulchitskaya:* Zhur. obshchei Khim. **26**, 208 (1956).
[19] *Ferenczi I., Zsolt J., Matkovics B.:* Acta Biol. Acad. Sci. Hung. (Under publication).
[20] *Vogel, A. I.:* Practical Organic Chemistry (Longmans, Green and Co., London, New-York, Toronto 1956).
[21] *Gabriel, S.:* Chem. Ber. **20**, 2227 (1887).